

## COMMENTARY TO HABILITATION THESIS

**Mgr. Karel Souček, Ph.D.**

### **Plasticity of cell identity and its role in cancer progression**

Cancer remains a formidable global health challenge, contributing significantly to morbidity and mortality worldwide. Despite substantial progress in cancer research and treatment, the intricate nature of this disease presents significant obstacles in developing effective therapies. Cancer cell plasticity and tumor heterogeneity have garnered considerable attention in cancer biology. This attention is driven by recognizing their crucial roles in cancer progression, resistance to treatment, metastasis, and the recurrence of the disease. This thesis briefly summarizes our current understanding of cell plasticity and tumor heterogeneity and specifies the author's contribution.

The first chapter focuses on the regulation of cell signaling and tumor suppression in the context of epithelial-mesenchymal plasticity. Special attention is paid to the dual role of TGF- $\beta$  in suppressing and promoting cancer and its interaction with other signaling pathways, e.g., IL-6/STAT3. Our research findings offer valuable insights into the complex molecular mechanisms that drive cancer progression and suggest potential avenues for targeted therapeutic interventions. The second chapter is dedicated to neuroendocrine differentiation and senescence in the context of androgen depletion in prostate cancer. We showed that prostate cancer cells exhibit plasticity during androgen depletion therapy (ADT), often transdifferentiating into neuroendocrine prostate cancer (NEPC), contributing to treatment resistance. Additionally, we showed that cell cycle modulation, senescence, and the senescence-associated secretory phenotype are implicated in promoting NEPC. These findings underscore the complexity of prostate cancer plasticity and emphasize the need for comprehensive approaches to diagnosis and therapy. The third chapter discusses the role of epithelial-mesenchymal transition (EMT) in dissemination. Here, we brought more understanding of EMT in cancer and revealed a complex regulatory network involving factors like TGF- $\beta$ , p53, MDM2, and Trop2. These findings provide better insight into cancer development and suggest a pathway for new therapeutic strategies targeting tumor-initiating cells. A significant technological opportunity to accurately identify cell subtypes and phenotypic markers and improve our understanding of tumor heterogeneity and microenvironment is discussed in the context of our result in the final chapter.

The following articles represent the author's contribution to the understanding of cell plasticity and cancer heterogeneity. It includes 19 primary research articles, two book chapters, and five reviews (out of 140 author's publication records available on WOS on January 31st, 2024) related to habilitation. The author's contribution is summarized in the tables below.

[1] Vanhara P, Lincova E, Kozubik A, Jurdic P, **Soucek K\***, Smarda J. Growth/differentiation factor-15 inhibits differentiation into osteoclasts-A novel factor involved in control of osteoclast differentiation. *Differentiation* 2009;**78**: 213-22. \*shared corresponding author. *Impact factor (WOS, 2008): 3,180, Q2. Number of citations (WOS, 2023): 36*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	50	30	50

[2] Starsichova A, Lincova E, Pernicova Z, Kozubik A, **Soucek K**. TGF- $\beta$  1 suppresses IL-6-induced STAT3 activation through regulation of Jak2 expression in prostate epithelial cells. *Cellular Signalling* 2010;**22**: 1734-44. *Impact factor (WOS, 2009): 4,094, Q2. Number of citations (WOS, 2023): 25*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	100	90	100

[3] Pernicova Z, Slabakova E, Kharashvili G, Bouchal J, Kral M, Kunicka Z, Machala M, Kozubik A, **Soucek K**. Androgen Depletion Induces Senescence in Prostate Cancer Cells through Down-regulation of Skp2. *Neoplasia* 2011;**13**: 526-36. *Impact factor (WOS, 2010): 5,476, Q1. Number of citations (WOS, 2023): 59*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	90	50	75

[4] Slabakova E, Pernicova Z, Slavickova E, Starsichova A, Kozubik A, **Soucek K**. TGF- $\beta$ 1-Induced EMT of Non-Transformed Prostate Hyperplasia Cells Is Characterized by Early Induction of SNAI2/Slug. *Prostate* 2011;**71**: 1332-43. *Impact factor (WOS, 2010): 3,377, Q1. Number of citations (WOS, 2023): 83*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
5	100	50	75

[5] Knopfova L, Benes P, Pekarcikova L, Hermanova M, Masarik M, Pernicova Z, **Soucek K**, Smarda J. c-Myb regulates matrix metalloproteinases 1/9, and cathepsin D: implications for matrix-dependent breast cancer cell invasion and metastasis. *Molecular Cancer* 2012;**11**. *Impact factor (WOS, 2011): 3,993, Q1. Number of citations (WOS, 2023): 53*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
5	5	5	5

[6] Vanhara P, Hampl A, Kozubik A, **Soucek K**. Growth/differentiation factor-15: prostate cancer suppressor or promoter? *Prostate Cancer and Prostatic Diseases* 2012;**15**: 320-8. *Impact factor (WOS, 2011): 2,421, Q2. Number of citations (WOS, 2023): 50*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
0, review	75	50	75

[7] Fedr R, Pernicova Z, Slabakova E, Strakova N, Bouchal J, Grepl M, Kozubik A, Soucek K. Automatic cell cloning assay for determining the clonogenic capacity of cancer and cancer stem-like cells. *Cytometry A* 2013;**83A**: 472-82. *Impact factor (WOS, 2012): 3,711, Q2. Number of citations (WOS, 2023): 26*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	90	75	90

[8] Pernicova Z, Vanhara P, **Soucek K**. Formation of secretory senescent cells in prostate tumors: the role of androgen receptor activity and cell cycle regulation. In: *Tumor Dormancy, Quiescence, and Senescence, Volume 1: Aging, Cancer, and Noncancer Pathologies*, Springer Netherlands, 2013: 303-16.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
0, book chapter	100	50	75

[9] Pernicova Z, Slabakova E, Fedr R, Simeckova S, Jaros J, Suchankova T, Bouchal J, Kharraishvili G, Kral M, Kozubik A, **Soucek K**. The role of high cell density in the promotion of neuroendocrine transdifferentiation of prostate cancer cells. *Molecular Cancer* 2014;**13**: 113. *Impact factor (WOS, 2013): 5,397, Q1. Number of citations (WOS, 2023): 25*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
5	80	75	75

[10] Kratochvilova K, Horak P, Esner M, **Soucek K**, Pils D, Anees M, Tomasich E, Drafi F, Jurtikova V, Hampl A, Krainer M, Vanhara P. Tumor suppressor candidate 3 (TUSC3) prevents the epithelial-to-mesenchymal transition and inhibits tumor growth by modulating the endoplasmic reticulum stress response in ovarian cancer cells. *Int J Cancer* 2015;**137**: 1330-1340. *Impact factor (WOS, 2014): 5,085, Q1. Number of citations (WOS, 2023): 37*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
0	5	10	10

[11] Slabakova E, Kharraishvili G, Smejova M, Pernicova Z, Suchankova T, Remsik J, Lerch S, Strakova N, Bouchal J, Kral M, Culig Z, Kozubik A, **Soucek K**. Opposite regulation of MDM2 and MDMX expression in acquisition of mesenchymal phenotype in benign and cancer cells. *Oncotarget* 2015;**6**: 36156-71. *Impact factor (WOS, 2014): 6,359, Q1. Number of citations (WOS, 2023): 16*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
5	90	50	75

**[12]** Slabakova E, Culig Z, Remsik J, **Soucek K**. Alternative mechanisms of miR-34a regulation in cancer. *Cell Death & Disease* 2017;**8**. *Impact factor (WOS, 2016): 5,965, Q1. Number of citations (WOS, 2023): 183*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
0, review	75	30	50

**[13]** Kahounova Z, Kurfurstova D, Bouchal J, Kharraishvili G, Navratil J, Remsik J, Simeckova S, Student V, Kozubik A, **Soucek K**. The fibroblast surface markers FAP, anti-fibroblast, and FSP are expressed by cells of epithelial origin and may be altered during epithelial-to-mesenchymal transition. *Cytometry A* 2018;**93**: 941-51. *Impact factor (WOS, 2017): 3,260, Q2. Number of citations (WOS, 2023): 45*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	80	50	75

**[14]** Knopfova L, Biglieri E, Volodko N, Masarik M, Hermanova M, Glaus Garzon JF, Ducka M, Kucirkova T, **Soucek K**, Smarda J, Benes P, Borsig L. Transcription factor c-Myb inhibits breast cancer lung metastasis by suppression of tumor cell seeding. *Oncogene* 2018;**37**: 1020-30. *Impact factor (WOS, 2017): 6,854, Q1. Number of citations (WOS, 2023): 15*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
5	0	10	10

**[15]** Remsik J, Bino L, Kahounova Z, Kharraishvili G, Simeckova S, Fedr R, Kucirkova T, Lenart S, Muresan XM, Slabakova E, Knopfova L, Bouchal J, Kral M, Benes P, **Soucek K**. Trop-2 plasticity is controlled by epithelial-to-mesenchymal transition. *Carcinogenesis* 2018;**39**: 1411-1418. *Impact factor (WOS, 2017): 5,072, Q1. Number of citations (WOS, 2023): 18*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
5	90	30	80

**[16]** Remsik J, Fedr R, Navratil J, Bino L, Slabakova E, Fabian P, Svoboda M, **Soucek K**. Plasticity and intratumoural heterogeneity of cell surface antigen expression in breast cancer. *British Journal of Cancer* 2018;**118**: 813-819. *Impact factor (WOS, 2017): 5,922, Q1. Number of citations (WOS, 2023): 17*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
5	90	30	80

**[17]** Simeckova S, Fedr R, Remsik J, Kahounova Z, Slabakova E, **Soucek K**. Multiparameter cytometric analysis of complex cellular response. *Cytometry A* 2018;**93**: 239-248. *Impact factor (WOS, 2018): 3,260. Number of citations (Google Scholar, 2023): 2*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	90	75	90

[18] Simeckova S, Kahounova Z, Fedr R, Remsik J, Slabakova E, Suchankova T, Prochazkova J, Bouchal J, Kharashvili G, Kral M, Benes P, **Soucek K**. High Skp2 expression is associated with a mesenchymal phenotype and increased tumorigenic potential of prostate cancer cells. *Sci Rep* 2019;**9**: 5695. *Impact factor (WOS, 2018): 4,011, Q1. Number of citations (WOS, 2023): 20*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
5	90	75	90

[19] Drapela S, Bouchal J, Jolly MK, Culig Z, **Soucek K**. ZEB1: A Critical Regulator of Cell Plasticity, DNA Damage Response, and Therapy Resistance. *Front Mol Biosci* 2020;**7**: 36. *Impact factor (WOS, 2019): 4,188, Q2. Number of citations (WOS, 2023): 90*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
0, review	90	30	75

[20] Lenart S, Lenart P, Smarda J, Remsik J, **Soucek K**, Benes P. Trop2: Jack of All Trades, Master of None. *Cancers (Basel)* 2020;**12**: 3328. *Impact factor (WOS, 2020): 6,126, Q1. Number of citations (WOS, 2023): 46*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
0, review	5	25	25

[21] Remsik J, Pickova M, Vacek O, Fedr R, Bino L, Hampl A, **Soucek K**. TGF- $\beta$  regulates Sca-1 expression and plasticity of pre-neoplastic mammary epithelial stem cells. *Sci Rep* 2020;**10**: 11396. *Impact factor (WOS, 2020): 3,998, Q1. Number of citations (WOS, 2023): 4*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
5	90	30	50

[22] Kvokackova B, Remsik J, Jolly MK, **Soucek K**. Phenotypic Heterogeneity of Triple-Negative Breast Cancer Mediated by Epithelial-Mesenchymal Plasticity. *Cancers (Basel)* 2021;**13**: 2188. *Impact factor (WOS, 2020): 6,639, Q1. Number of citations (WOS, 2023): 31*

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
0, review	90	20	60

[23] Drapela S, Fedr R, Vacek O, Remsik J, **Soucek K**. High-Throughput, Parallel Flow Cytometry Screening of Hundreds of Cell Surface Antigens Using Fluorescent Barcoding. *Methods Mol Biol* 2022;**2543**: 99-111.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
0	100	30	90

[24] Muresan XM, Slabakova E, Prochazkova J, Drapela S, Fedr R, Pickova M, Vacek O, Vichova R, Suchankova T, Bouchal J, Kurfurstova D, Kral M, Hulinova T, Sykora RP, Student V, Hejret V, van Weerden WM, Puh M, Pustka V, Potesil D, Zdrahal Z, Culig Z,

**Soucek K.** Toll-Like Receptor 3 Overexpression Induces Invasion of Prostate Cancer Cells, whereas Its Activation Triggers Apoptosis. *Am J Pathol* 2022;**192**: 1321-35. Impact factor (WOS, 2022): 5,770, Q1. Number of citations (WOS, 2023): 2

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	90	30	75

**[25]** Rihova K, Ducka M, Zambo IS, Vymetalova L, Sramek M, Trcka F, Verner J, Drapela S, Fedr R, Suchankova T, Pavlatovska B, Ondrouskova E, Kubelkova I, Zapletalova D, Tucek S, Mudry P, Krakorova DA, Knopfova L, Smarda J, **Soucek K**, Borsig L, Benes P. Transcription factor c-Myb: novel prognostic factor in osteosarcoma. *Clin Exp Metastasis* 2022;**39**: 375-90. Impact factor (WOS, 2021): 4,510, Q2. Number of citations (WOS, 2023): 3

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
0	0	10	10

**[26]** Kvokackova B, Fedr R, Kuzilkova D, Stuchly J, Vavrova A, Navratil J, Fabian P, Ondrussek R, Ovesna P, Remsik J, Bouchal J, Kalina T, **Soucek K**. Single-cell protein profiling defines cell populations associated with triple-negative breast cancer aggressiveness. *Molecular Oncology* 2023;**17**: 1024-40. Impact factor (WOS, 2021): 6,6, Q1. Number of citations (WOS, 2023): 1

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
0	75	30	75